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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/089948 A1

(54) Title: NOVEL CRYSTALLINE FORMS OF ZIPRASIDONE HYDROCHLORIDE

(57) Abstract: The present invention provides novel crystalline forms of ziprasidone hydrochloride monohydrate, processes for their preparation and pharmaceutical compositions containing them.

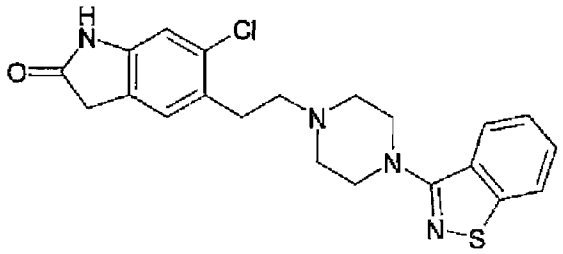
NOVEL CRYSTALLINE FORMS OF ZIPRASIDONE HYDROCHLORIDE

FIELD OF THE INVENTION

The present invention provides novel crystalline forms of ziprasidone hydrochloride monohydrate, processes for their preparation and pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Ziprasidone of formula (1) :



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or 5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one and its salts are antipsychotic agents. Ziprasidone hydrochloride and related compounds and their therapeutic uses are disclosed in US 4,831,031.

The crystalline forms of ziprasidone mesylate were reported in WO 97/42190, WO 97/42191.

It has now been discovered that ziprasidone hydrochloride monohydrate can be prepared in three stable crystalline forms having good dissolution characteristics.

The object of the present invention is to provide stable novel crystalline forms of ziprasidone hydrochloride monohydrate, processes for preparing these forms and pharmaceutical compositions containing them.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of ziprasidone hydrochloride monohydrate, designated as form I,

characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 10.9, 13.9, 15.9, 16.4, 17.5, 19.2, 20.6, 21.3, 21.9, 24.2, 24.7, 24.9, 25.7, 25.9 and 28.9 degrees. Figure 1 shows typical form I x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of ziprasidone hydrochloride monohydrate form I. Thus, a mixture of ziprasidone free base, hydrochloric acid and water is heated to about 45°C to 100°C; and ziprasidone hydrochloride monohydrate form I is isolated by filtration or centrifugation. Preferably, the mixture of ziprasidone free base, hydrochloric acid and water is heated to about 55°C to 65°C; and ziprasidone hydrochloride monohydrate form I is isolated by filtration or centrifugation.

In accordance with the present invention, there is provided a novel crystalline form of ziprasidone hydrochloride monohydrate, designated as form II, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 10.9, 11.3, 18.1, 19.5, 21.9, 23.7, 24.4, 24.8 and 26.2 degrees. Figure 2 shows typical form II x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of ziprasidone hydrochloride monohydrate form II. Thus, ziprasidone free base, an alcohol or a mixture of alcohols, dimethylformamide, a chlorinated solvent, hydrochloric acid and water are mixed to form a solution of ziprasidone hydrochloride; and the solvents are removed by the techniques such as vacuum drying, spray drying, freeze drying and lyophilization to form ziprasidone hydrochloride monohydrate form II. Water may be directly mixed or it may be mixed, for example, as an aqueous solution of hydrochloric acid. The alcohols are selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol. The preferable alcohols are methanol and ethanol. The chlorinated solvents are selected from the group consisting of methylene dichloride, chloroform, carbon tetrachloride and ethylene dichloride. The preferable ester solvents are chloroform and methylene dichloride.

In accordance with the present invention, there is provided a novel crystalline form of ziprasidone hydrochloride monohydrate, designated as form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 10.9, 14.8, 15.9, 18.1, 19.5, 21.8, 24.3, 24.9, 25.9 and 26.5 degrees. Figure 3 shows typical form III x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of ziprasidone hydrochloride monohydrate form III. Thus ziprasidone free base, an ether solvent or a mixture of ether solvents, dimethylformamide, hydrochloric acid and water are mixed to form a solution of ziprasidone hydrochloride; and ziprasidone hydrochloride monohydrate form III is isolated from the solution. Water may be directly mixed or it may be mixed, for example, as an aqueous solution of hydrochloric acid. The ether solvents are selected from the group consisting of diethyl ether, diisopropyl ether and tert-butyl methyl ether. The preferable ether solvent is diethyl ether.

Ziprasidone free base used in the above processes can be obtained from the previously known methods.

In accordance with the present invention, there is provided a pharmaceutical composition comprising a crystalline form of ziprasidone hydrochloride monohydrate and pharmaceutically acceptable carrier or diluent. The crystalline form includes form I, form II or form III.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction spectrum of ziprasidone hydrochloride monohydrate form I.

Figure 2 is a x-ray powder diffraction spectrum of ziprasidone hydrochloride monohydrate form II.

Figure 3 is a x-ray powder diffraction spectrum of ziprasidone hydrochloride monohydrate form III.

X-Ray powder diffraction spectrum was measured on a Siemens D5000 x-ray powder diffractometer having a copper-Kα radiation.

The following examples further illustrate the present invention.

Example 1

Ziprasidone free base (10 gm), conc. hydrochloric acid (10 ml) and water (150 ml) are mixed and the reaction mass is heated to 60^{0}C and stirred for 4 hours at 60^{0}C to 65^{0}C. The contents are cooled to 25^{0}C, filtered, washed with water and dried to give 10 gm of ziprasidone hydrochloride monohydrate form I.

Example 2

Ziprasidone free base (2.5 gm), methanol (100 ml), dimethylformamide (100 ml), chloroform (25 ml) and conc. hydrochloric acid (1.5 ml) are mixed at 25°C. The contents are heated to 60°C and stirred for 10 minutes at 60°C to 65°C and the clear solution thus obtained is subjected to vacuum drying at 70°C for 40 hours to give ziprasidone hydrochloride monohydrate form II in near quantitative yield.

Example 3

Ziprasidone free base (3.0 gm), methanol (120 ml), dimethylformamide (100 ml), chloroform (30 ml) and conc. hydrochloric acid (1.5 ml) are mixed at 25°C. The contents are heated to 60°C and stirred for 10 minutes at 60°C to 65°C and the clear solution thus obtained is subjected to spray drying to give ziprasidone hydrochloride monohydrate form II.

Example 4

Ziprasidone free base(5.0 gm) is added to diethyl ether (50 ml) and heated to reflux temperature. Then dimethylformamide (145 ml) is added and the contents are stirred for 2 hours under reflux. Then conc. hydrochloric acid (2.5 ml) and water (3 ml) are added, and the solution is cooled to 25°C. The separated crystals are filtered to give 3.5 gm of ziprasidone hydrochloride monohydrate form III.

We claim:

1. A crystalline ziprasidone hydrochloride monohydrate form I, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 10.9, 13.9, 15.9, 16.4, 17.5, 19.2, 20.6, 21.3, 21.9, 24.2, 24.7, 24.9, 25.7, 25.9 and 28.9 degrees.
2. A crystalline ziprasidone hydrochloride monohydrate form I, further characterized by an x-ray powder diffraction spectrum as in figure 1.
3. A process for preparation of ziprasidone hydrochloride monohydrate form I as defined in claim 1, which comprises the steps of:

a) mixing ziprasidone free base, hydrochloric acid and water;
b) heating to about 45°C to 100°C; and
c) isolating ziprasidone hydrochloride monohydrate form I by filtration or centrifugation.

4. A process according to claim 3, wherein the reaction mass is heated to about 60°C to 65°C in (b).
5. A crystalline ziprasidone hydrochloride monohydrate form II, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 10.9, 11.3, 18.1, 19.5, 21.9, 23.7, 24.4, 24.8 and 26.2 degrees.
6. A crystalline ziprasidone hydrochloride monohydrate form II as defined in claim 5, further characterized by an x-ray powder diffraction spectrum as in figure 2.
7. A process for preparation of ziprasidone hydrochloride monohydrate form II as defined in claim 5, which comprises the steps of:

a) mixing ziprasidone free base, an alcohol or a mixture of alcohols, dimethylformamide, a chlorinated solvent, hydrochloric acid and water to form a ziprasidone hydrochloride solution; and
b) removing the solvents from the solution;

wherein the alcohol is selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol; and the chlorinated solvent is selected from the group consisting of methylene dichloride, chloroform, carbon tetrachloride and ethylene dichloride.

8. A process according to claim 7, wherein the solvents are removed by the techniques such as vacuum drying, spray drying, freeze drying and lyophilization.
9. A process according to claim 7, wherein the alcohol is methanol.
10. A process according to claim 7, wherein the chlorinated solvent is chloroform.
11. A crystalline ziprasidone hydrochloride monohydrate form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 10.9, 14.8, 15.9, 18.1, 19.5, 21.8, 24.3, 24.9, 25.9 and 26.5 degrees.
12. A crystalline ziprasidone hydrochloride monohydrate form III as defined in claim 11, further characterized by an x-ray powder diffraction spectrum as in figure 3.
13. A process for preparation of ziprasidone hydrochloride monohydrate form III as defined in claim 11, which comprises the steps of:

a) mixing ziprasidone free base, an ether solvent or a mixture of ether solvents, dimethylformamide, hydrochloric acid and water to form a ziprasidone hydrochloride solution; and

b) isolating ziprasidone hydrochloride monohydrate form III from the solution;

wherein the ether solvent is selected from the group consisting of diethyl ether, diisopropyl ether and tert-butyl methyl ether.

14. A process according to claim 11, wherein the ether solvent is diethyl ether.
15. A pharmaceutical composition comprising ziprasidone hydrochloride monohydrate form I of claim 1 and a pharmaceutically acceptable carrier or diluent.
16. A pharmaceutical composition comprising ziprasidone hydrochloride monohydrate form II of claim 5 and a pharmaceutically acceptable carrier or diluent.
17. A pharmaceutical composition comprising ziprasidone hydrochloride monohydrate form III of claim 11 and a pharmaceutically acceptable carrier or diluent.

fig. 1

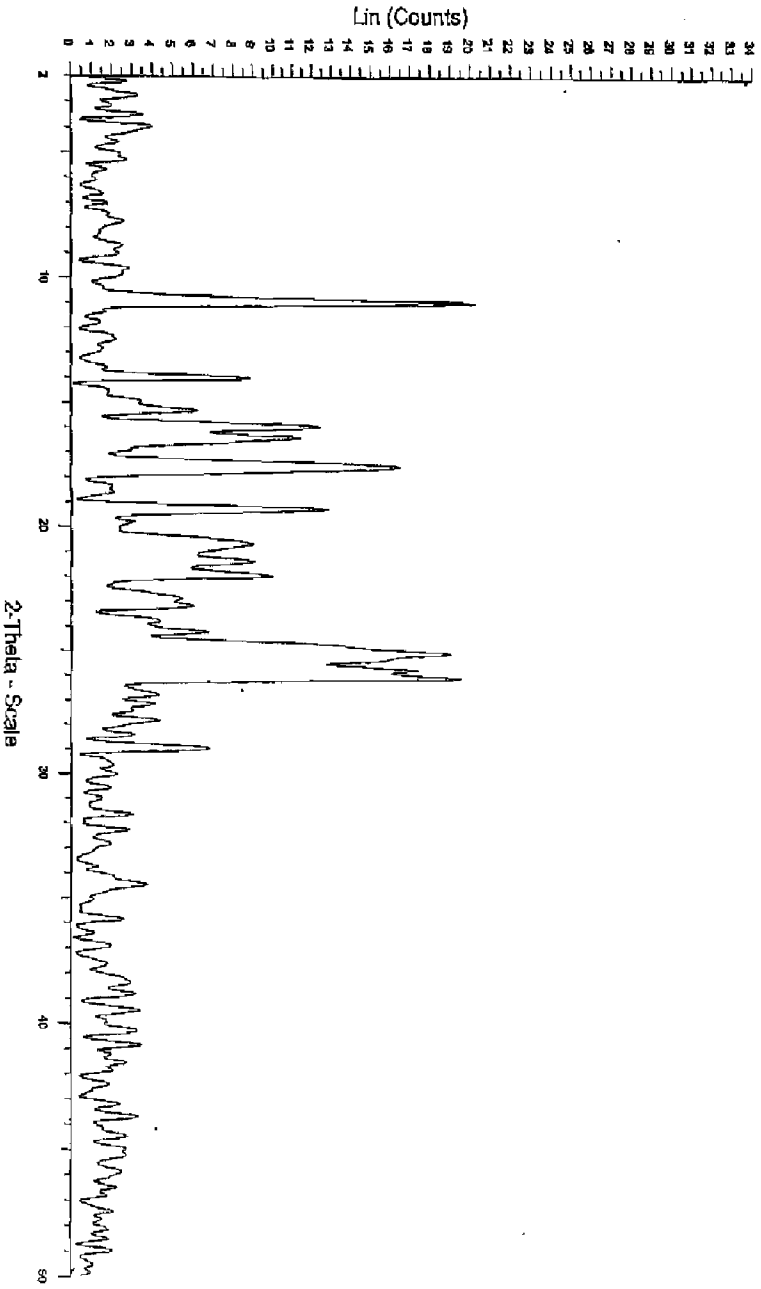


fig. 2

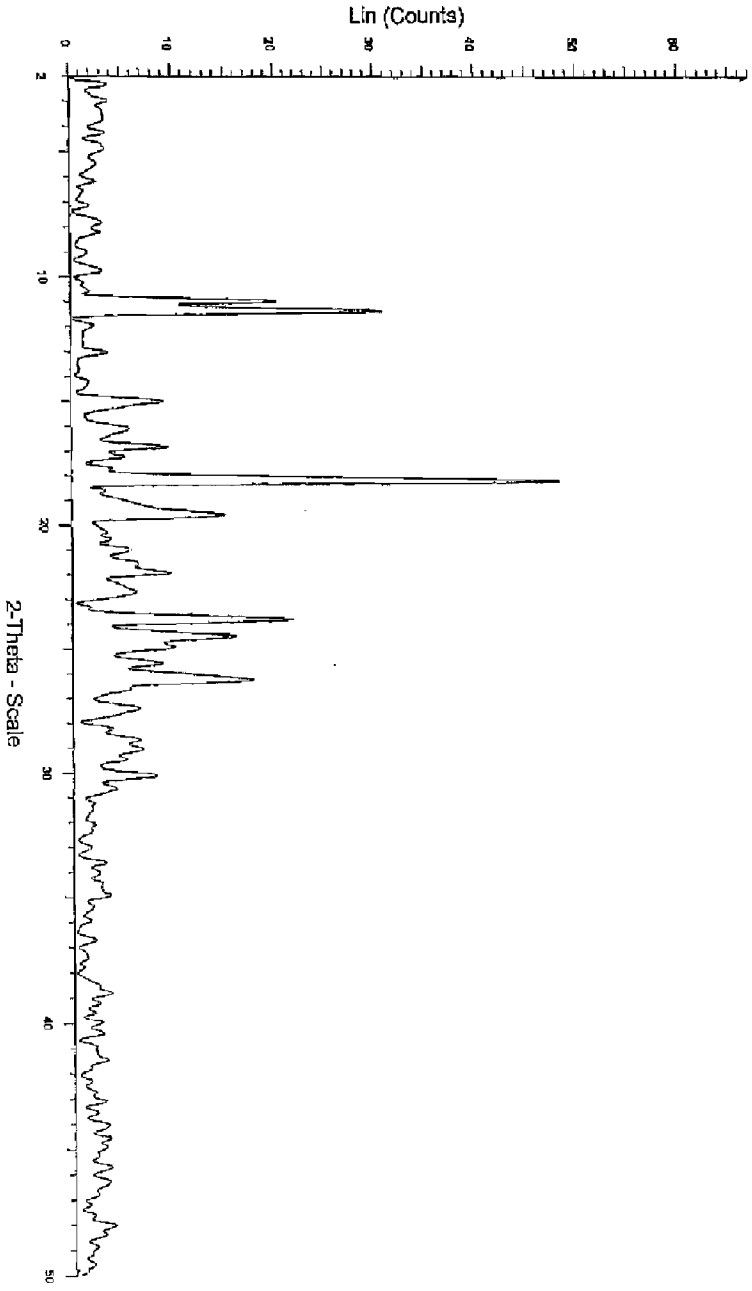
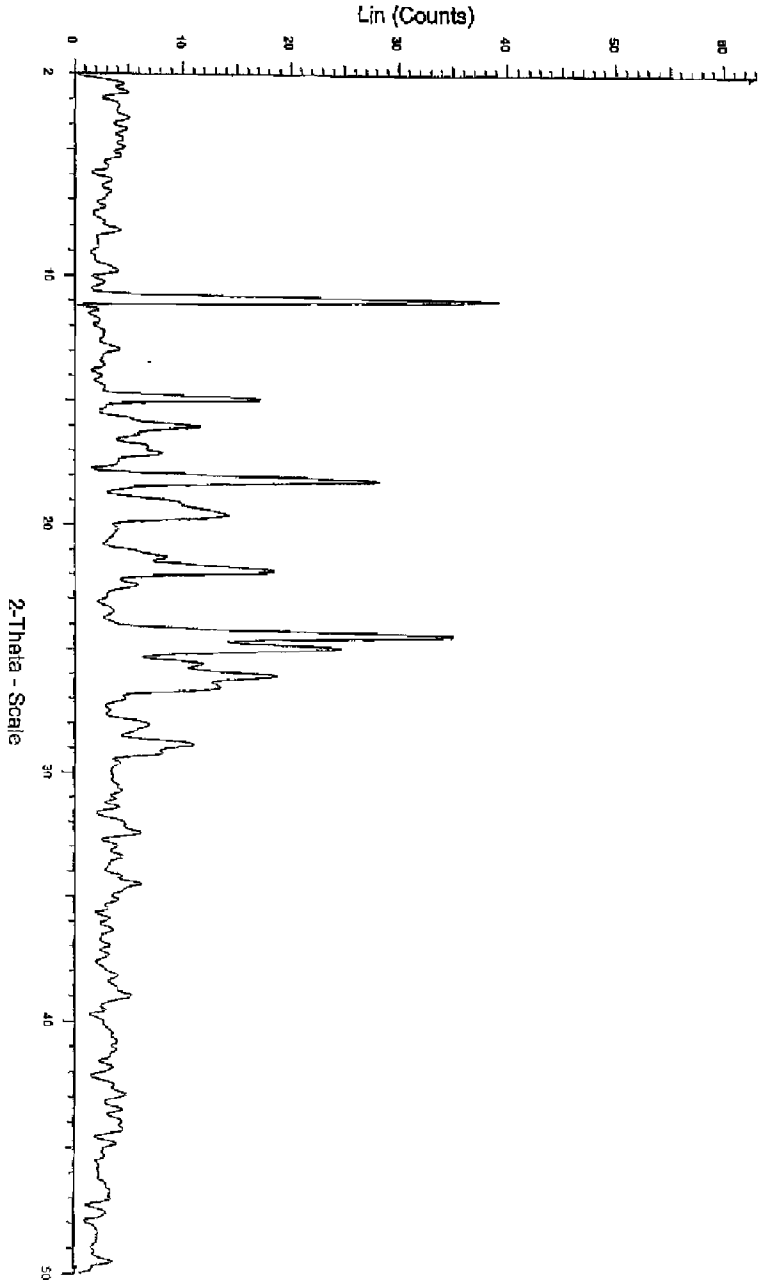


fig. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00154-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 417/12; A61K 31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE; STN Karlsruhe/Registry, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0586191 A1 (PFIZER INC.) 9 March 1994 (09.03.94) *abstract; page 2, line 23; page 2, lines 31-32; page 2, lines 40-44; page 2, line 50 - page 3, line 9; examples 1-3; claims 1,2,4.*	1,3,4,15
A		5,7-11,13, 14,16,17
X	EP 0584903 A1 (PFIZER INC.) 2 March 1994 (02.03.94) *page 4, line 56 - page 5, line 8; claims 12,20.*	1,3,4,15
A		5,7-11,13, 14,16,17
X	US 5338846 A (BUSCH et al.) 16 August 1994 (16.08.94) *column 1, lines 40-47; column 2, lines 64-66; column 3, lines 12-16; column 4, lines 3-14; claims 11,17,19.*	1,3,4,15
A		5,7-11,13, 14,16,17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2003 (10.12.2003)	11 February 2004 (11.02.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer KOLLER G. Telephone No. 1/53424/458

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00154-0

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2, 6, 12
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 2, 6, 12 refer to figures of the drawings and contravene Rule 6.2(a) PCT.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 03/00154-0

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP A 584903		AU B 642836	1993-10-28
		DE T 69330853T	2002-05-02
		PT T 584903T	2002-02-28
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		EG A 20251	1998-05-31
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